METRUM
RESEARCH GROUP

Bayesian analysis in NONMEM

Tim Waterhouse
Metrum Research Group

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Acknowledgments

These slides borrow heavily from the following:

- Introduction to Bayesian pharmacometric data analysis with NONMEM (ACoP 2019 workshop by Bill Gillespie and Curtis Johnston)
- "Tutorial: Bayesian Estimation in NONMEM" by Curtis K. Johnston, Matthew Wiens, John Mondick, Jonathan French, Bill Gillespie (and myself) (manuscript submitted for publication)

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- Why Bayesian?

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- Example Bayesian analysis

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- Add **data** and you have all the ingredients of Bayesian data analysis.
- With Bayes Rule and suitable computation tools those components are combined to yield **posterior distributions** of model parameters and predictions.
- Those distributions permit probabilistic inferences directly relevant to decision-making.

Introduction to Bayesian statistical principles and methods

- Bayesian principles and methods provide a coherent framework for:
  - Quantifying uncertainty,
  - Making inferences in the presence of that uncertainty.
- It is also the basis for formal approaches to incremental model building, parameter estimation and other statistical inference as knowledge and data are accumulated.

The two core notions that distinguish Bayesian analysis are:

- Unknown quantities are viewed as random variables, i.e., they are described in terms of probability distributions.
- Bayes rule provides a formal mechanism for combining prior knowledge and new data.

Bayesian inference
Bayes Rule

Bayes Rule is the basis for inference about model parameters (θ) given data (y) and prior knowledge about model parameters ($p(\theta)$):

$$
\begin{aligned}
p(\theta|y) &= \frac{p(\theta)\, p(y|\theta)}{p(y)} = \frac{p(\theta)\, p(y|\theta)}{\int p(\theta)\, p(y|\theta)\, d\theta} \\
&\propto p(\theta)\, p(y|\theta)
\end{aligned}
$$

The p's are probabilities or probability densities of the specified random variables.

Bayesian modeling/inference process

1. Assess prior distribution $p(\theta)$
   - θ viewed as random variables
   - Subjective
   - Ideally base on all available evidence/knowledge (or belief)
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4. Calculate posterior predictive distribution $p(y_{new}|y)$.
   - Use for inferences regarding future observations

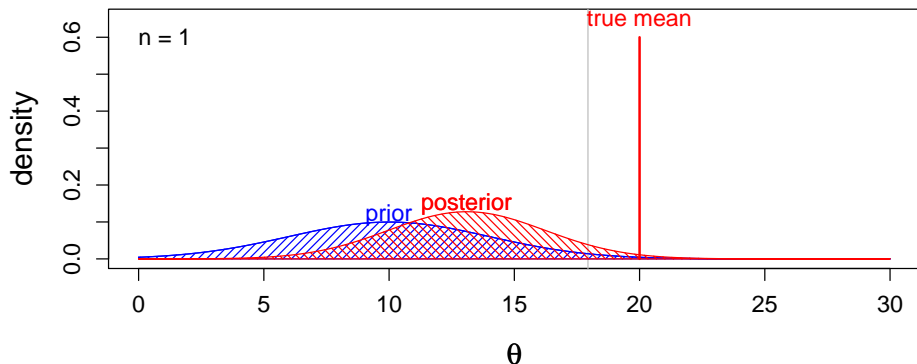$$p(y_{new}|y) = \int p(y_{new}|\theta)\, p(\theta|y)\, d\theta$$

A simple one parameter example

Estimating the mean of a normal distribution with a known variance where the prior is also normal:

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p(\theta|y) &\propto p(\theta)\, p(y|\theta) = p(\theta) \prod_{i=1}^{n} p(y_i|\theta) \\
&\propto \exp\left(-\frac{1}{2\tau_0^2}(\theta - \mu_0)^2\right) \prod_{i=1}^{n} \exp\left(-\frac{1}{2\sigma^2}(y_i - \theta)^2\right) \\
&\propto \exp\left(-\frac{1}{2}\left[\frac{1}{\tau_0^2}(\theta - \mu_0)^2 + \frac{1}{\sigma^2}\sum_{i=1}^{n}(y_i - \theta)^2\right]\right)
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$$\Downarrow$$

$$\theta|y \sim N(\mu_n, \tau_n)$$

$$\mu_n = \frac{\frac{1}{\tau_0^2}\mu_0 + \frac{n}{\sigma^2}\overline{y}}{\frac{1}{\tau_0^2} + \frac{n}{\sigma^2}} \quad \text{and} \quad \tau_n^2 = \frac{1}{\frac{1}{\tau_0^2} + \frac{n}{\sigma^2}}$$
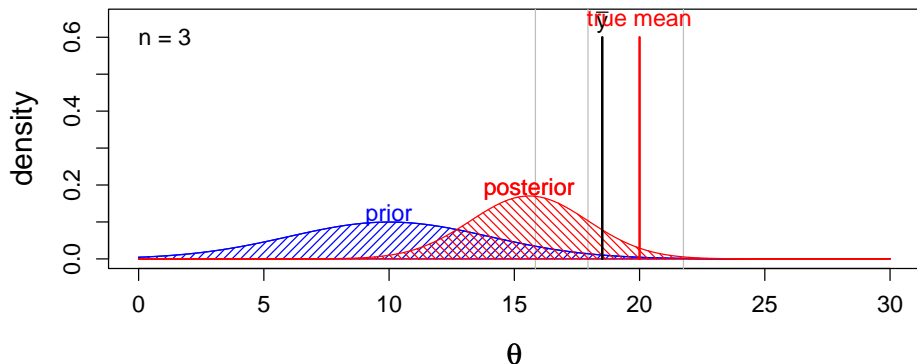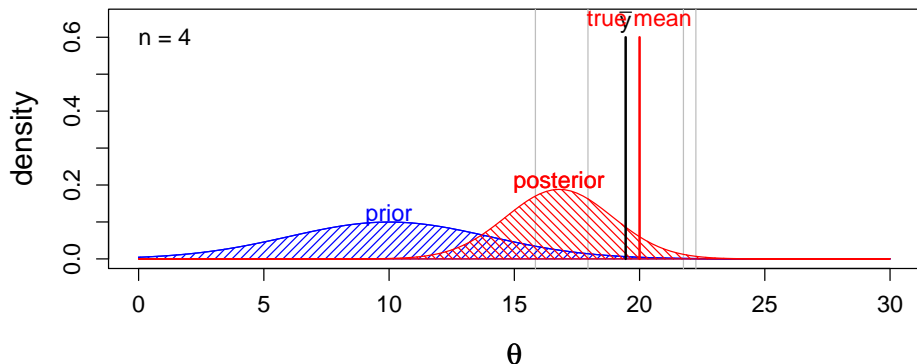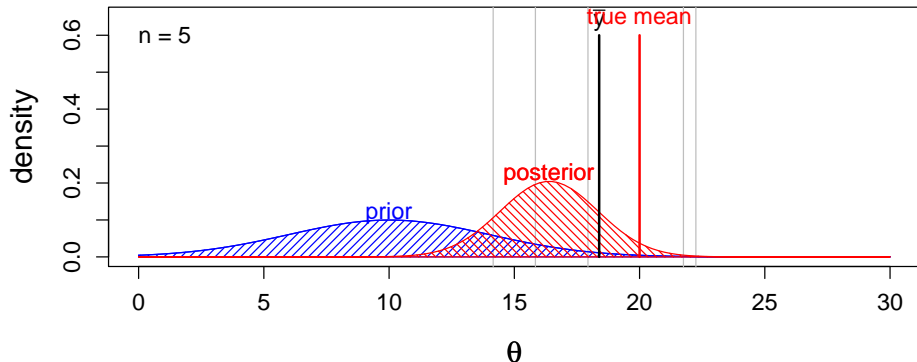
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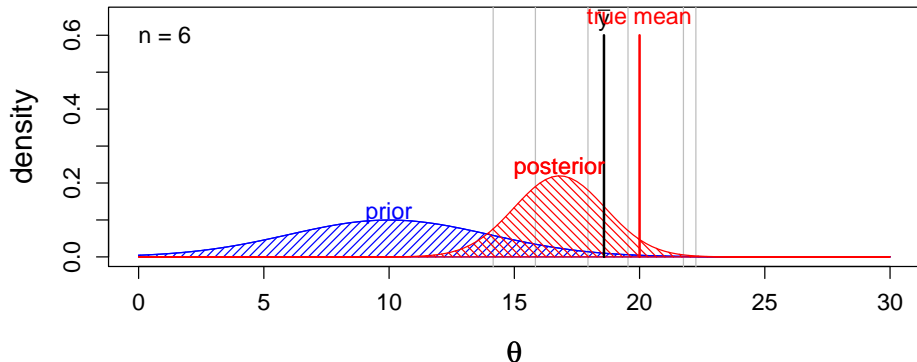
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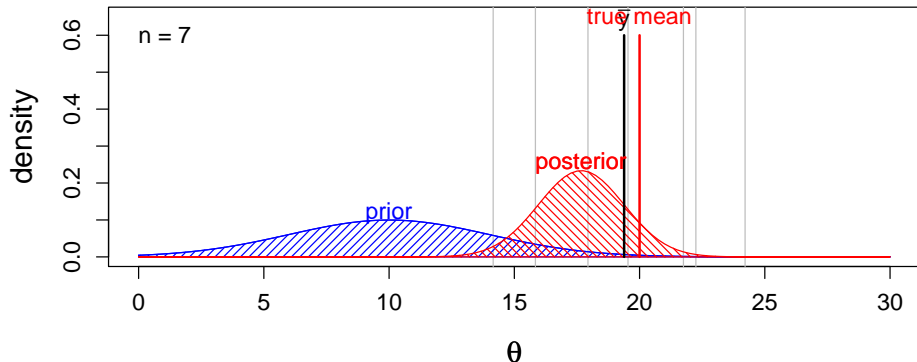
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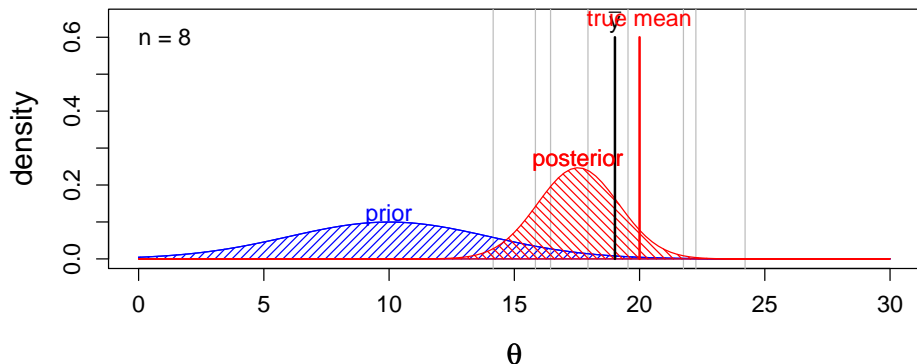
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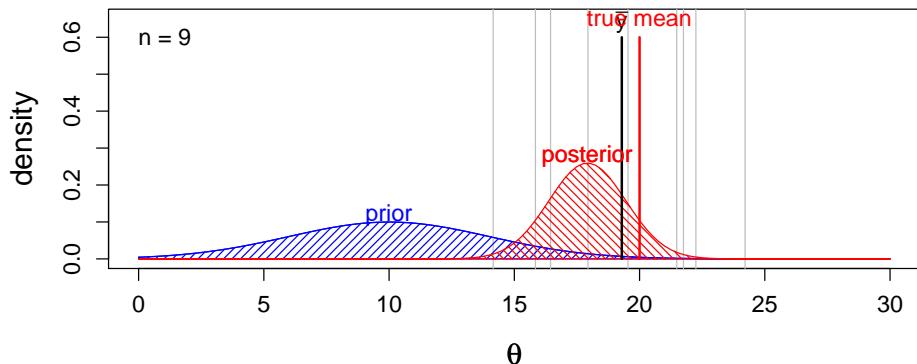
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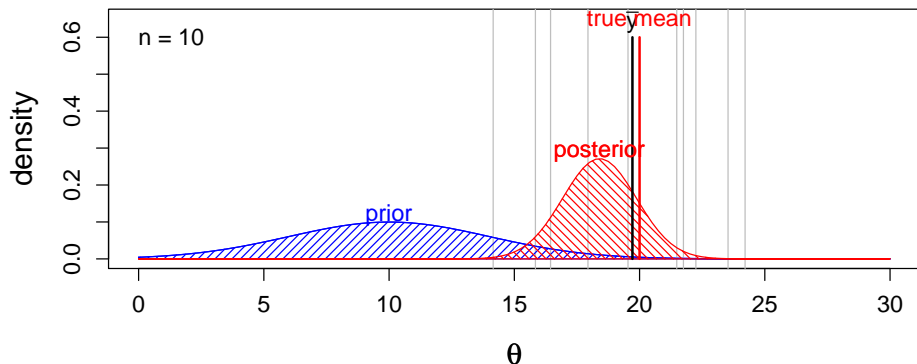
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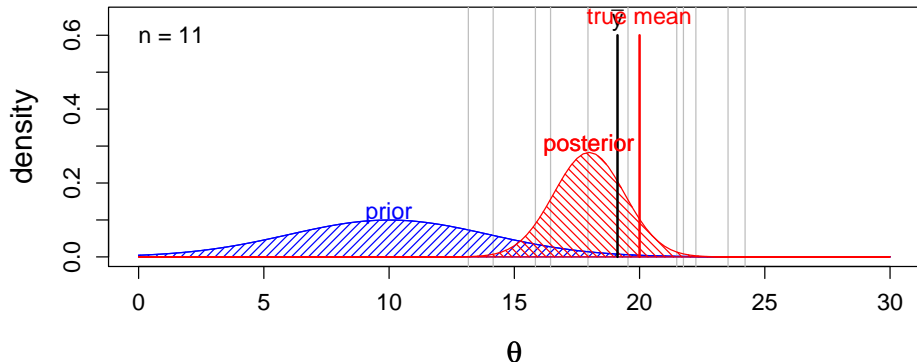
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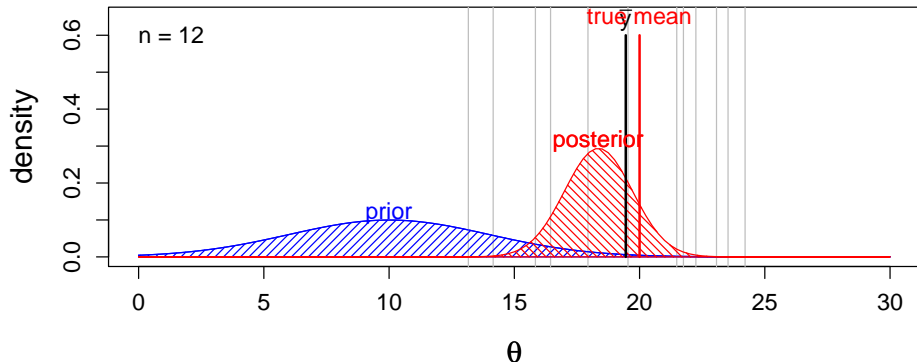
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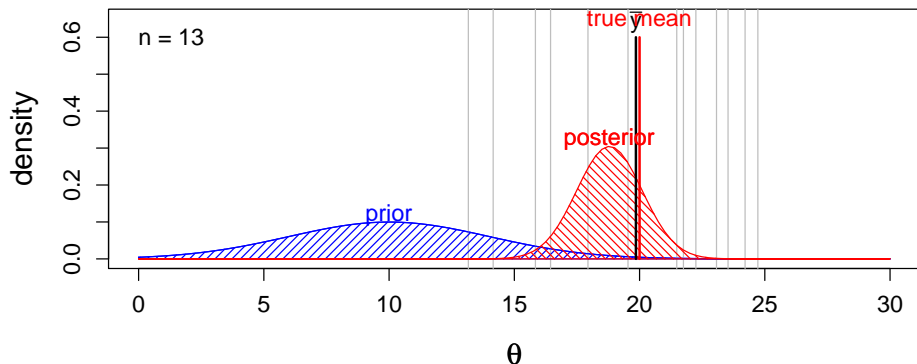
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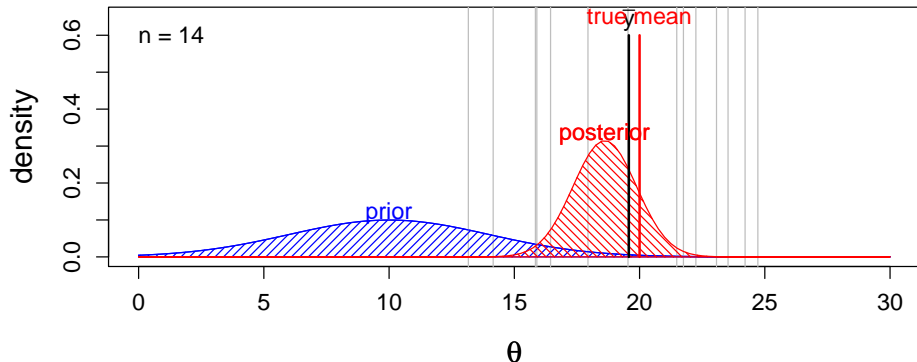
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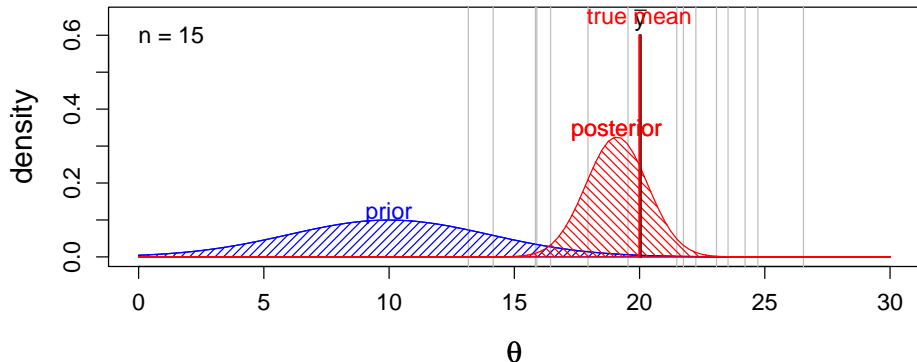
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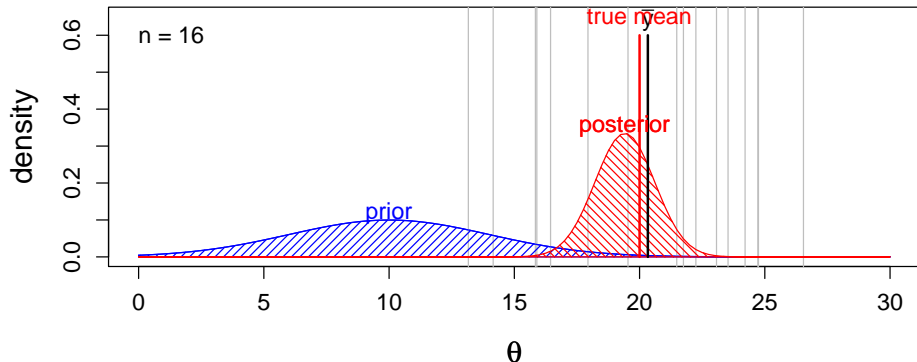
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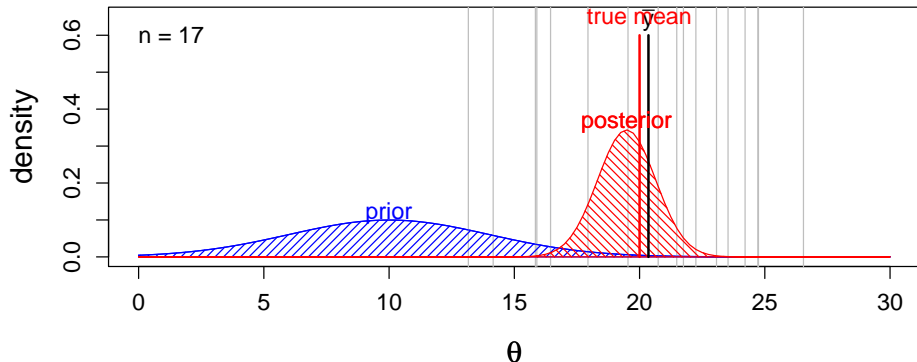
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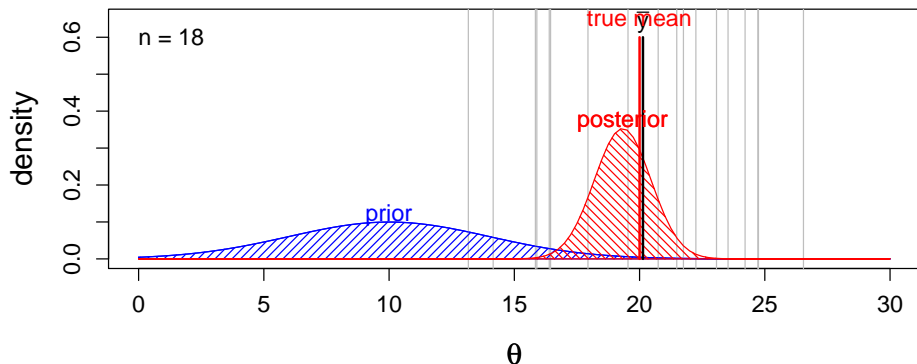
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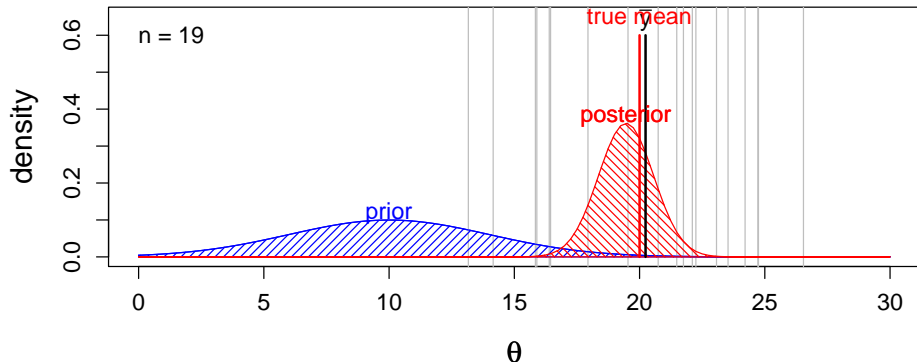
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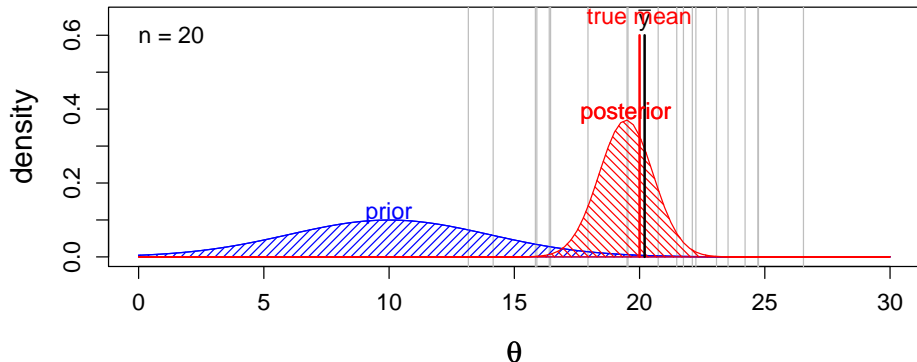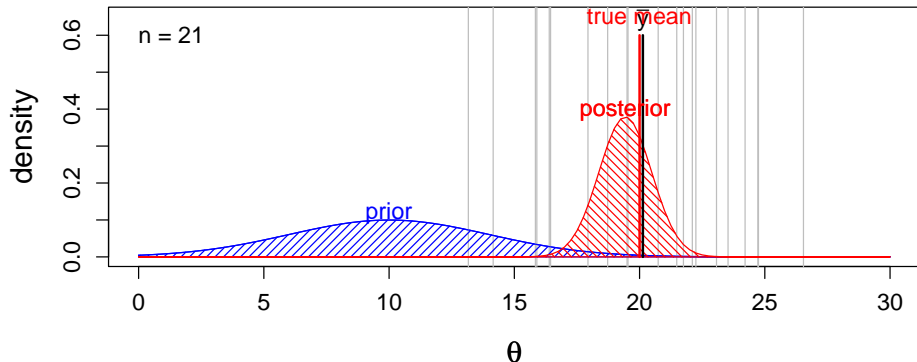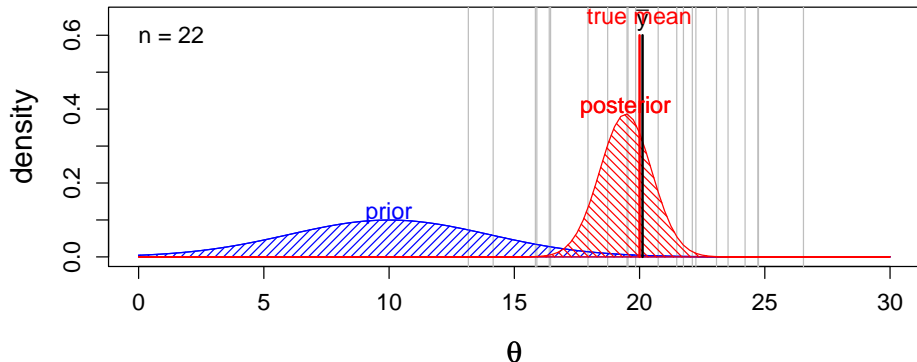
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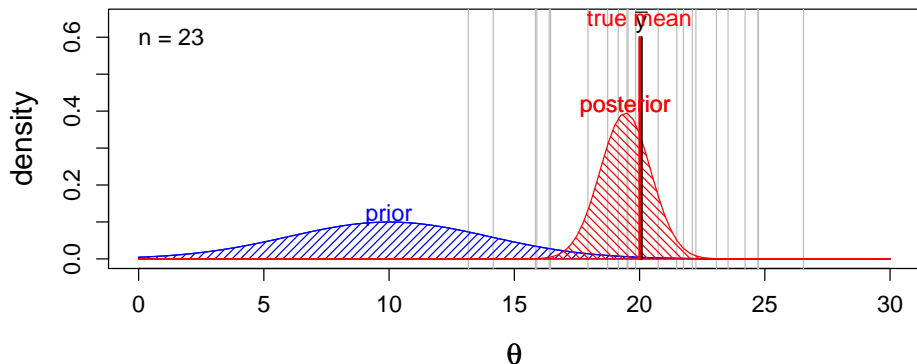
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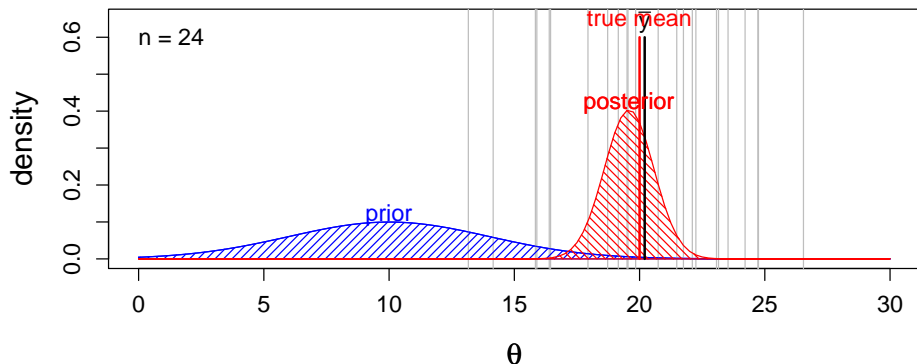
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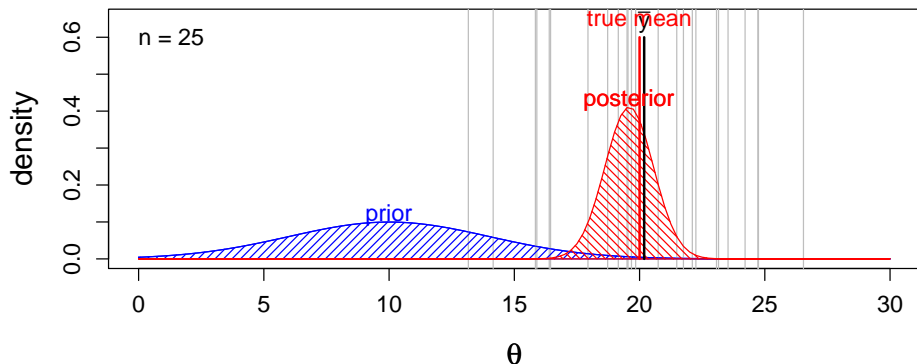
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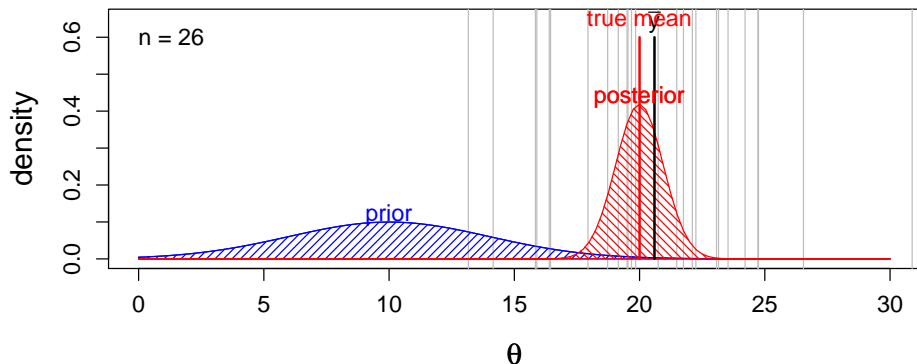
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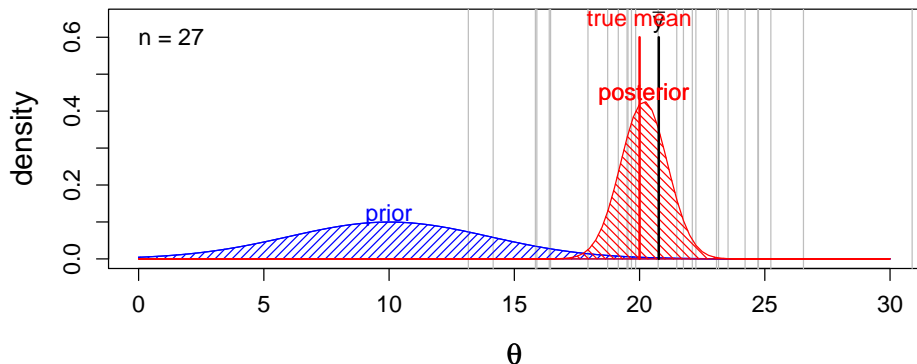
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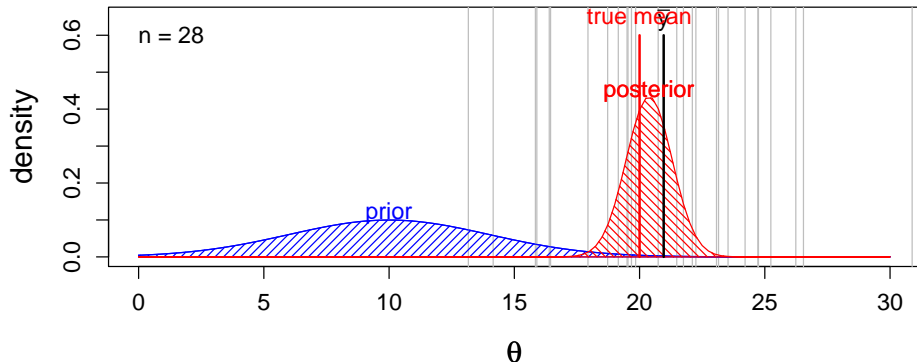
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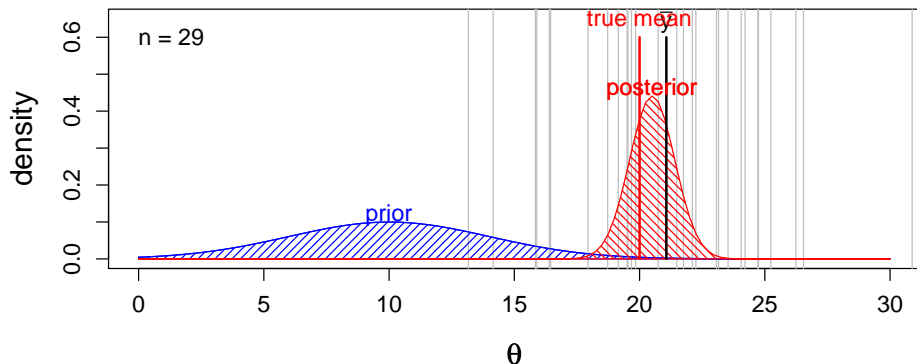
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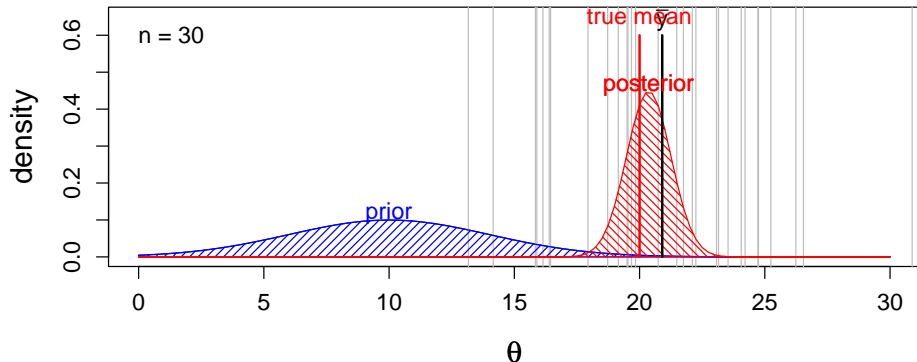
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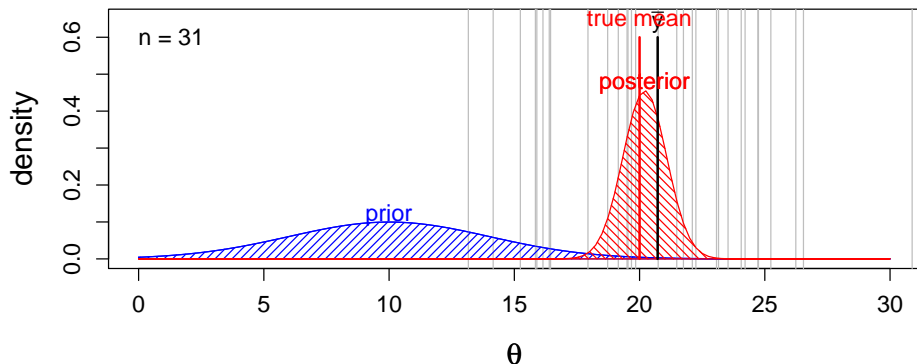
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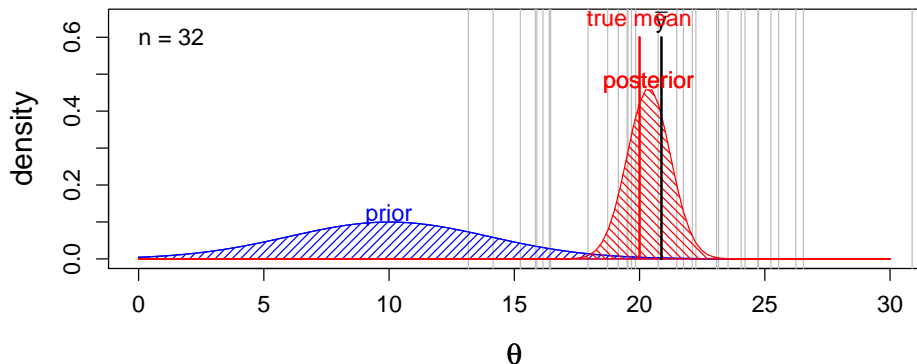
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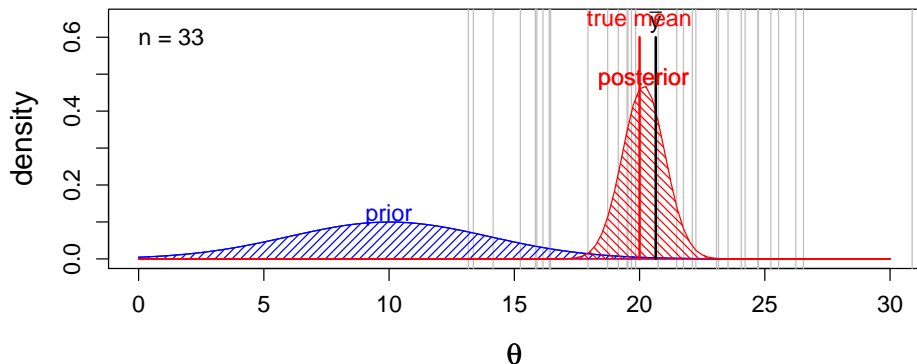
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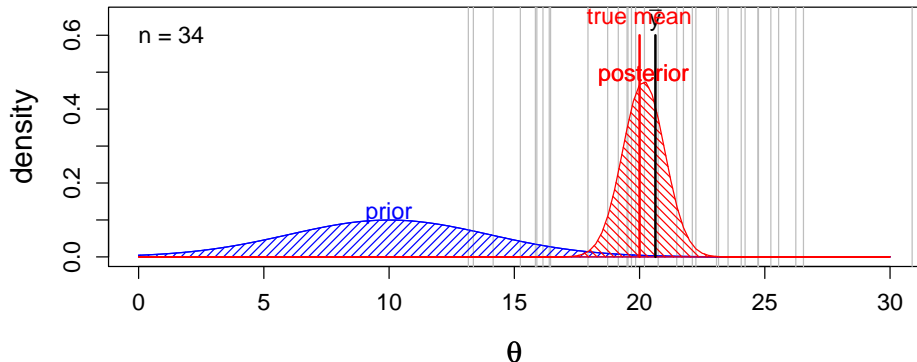
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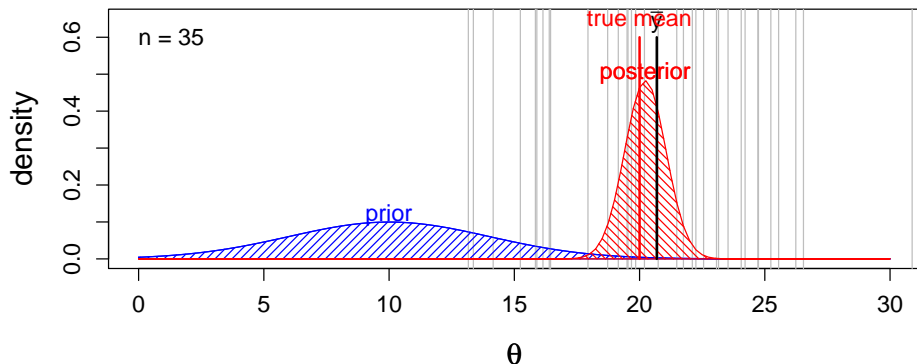
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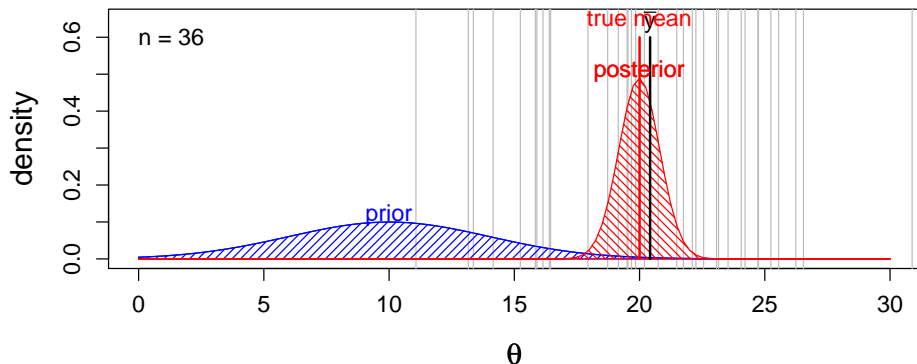
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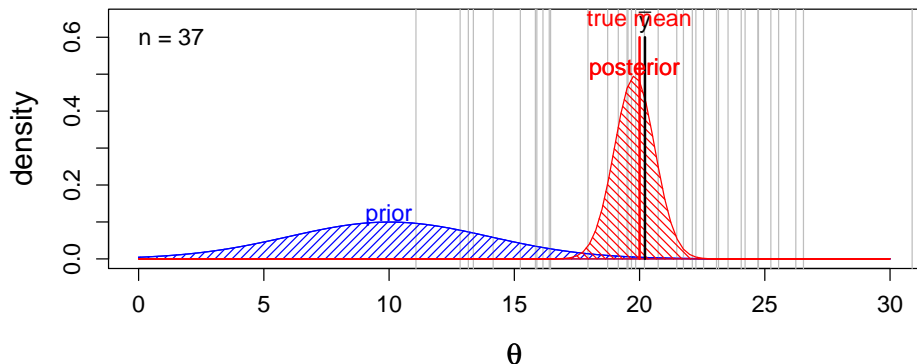
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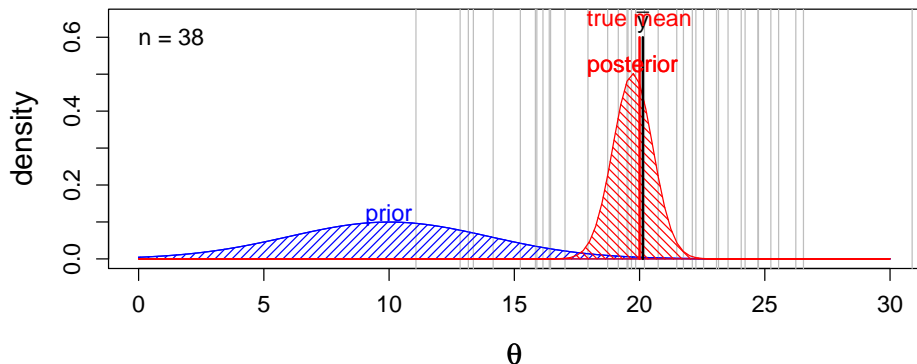
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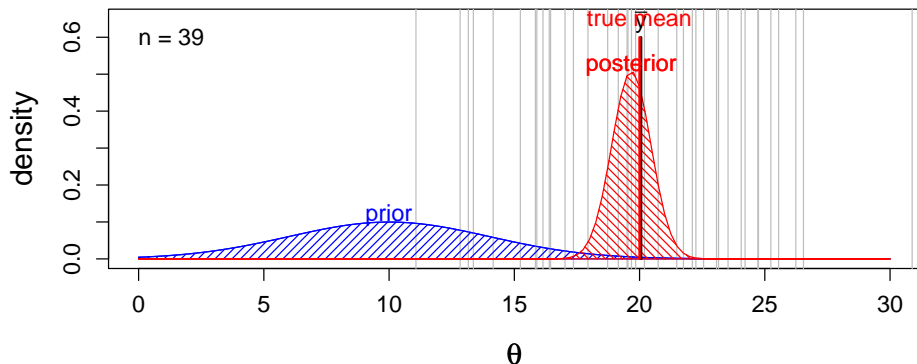
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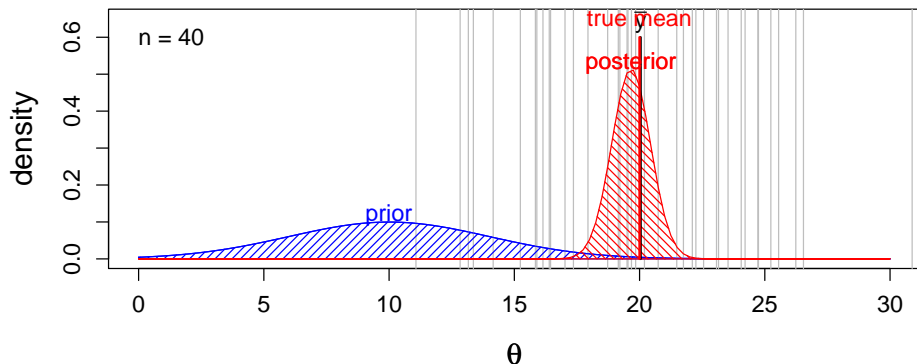
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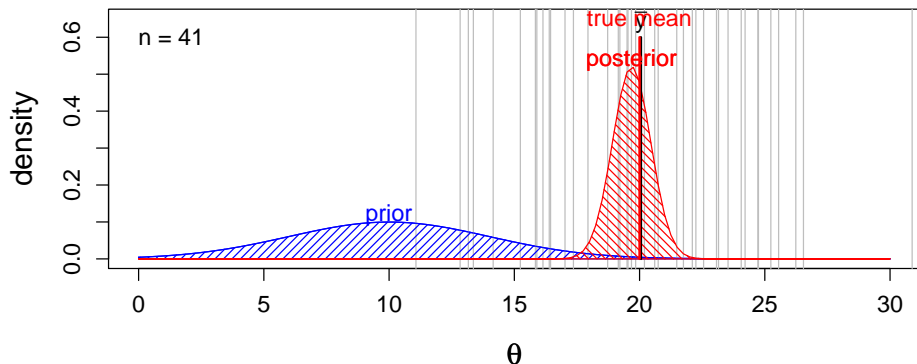
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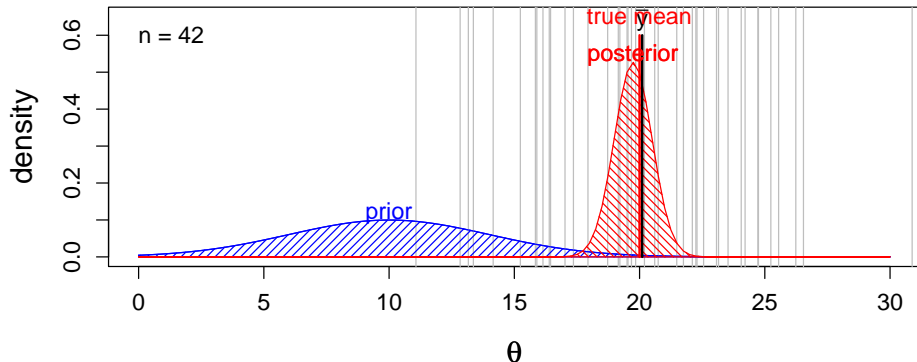
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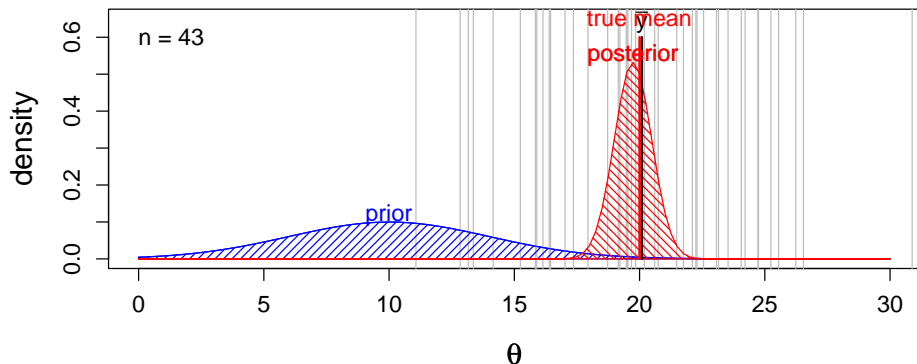
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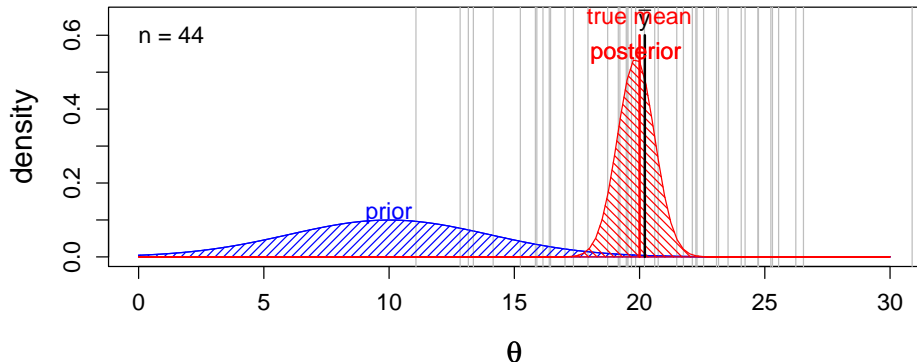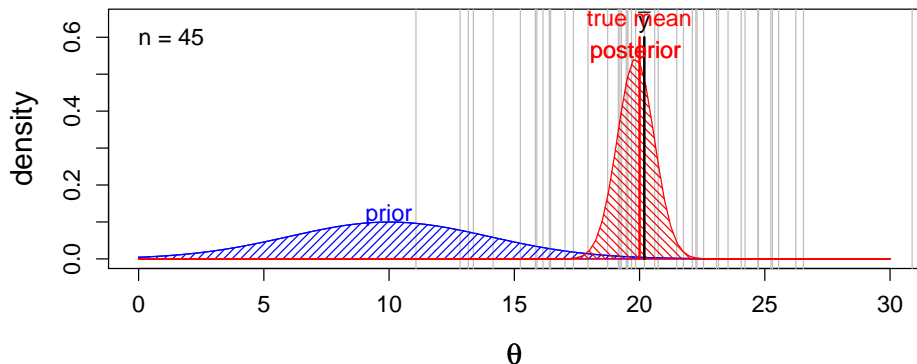
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- For most realistic problems, those are very computationally demanding tasks.
- Increases in computation speed and development of new algorithms over the last 25–30 years have finally made full Bayesian analysis a feasible option for routine data analysis.

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- For integrals in fewer dimensions, a numerical quadrature method might be practical.
- Now imagine the computational requirements for hierarchical models, e.g., population PK models, with individual-specific parameters in the hundreds!!

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- But how do you simulate samples from a high dimensional joint posterior distribution?
- Markov chain Monte Carlo (MCMC) simulation via NONMEM is one approach we will explore today.

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- Practical consequences:
  - Use only samples drawn after convergence is achieved, i.e., discard samples from a "warmup" phase.
  - Draw more samples than you would for independent random draws.

HMC performance
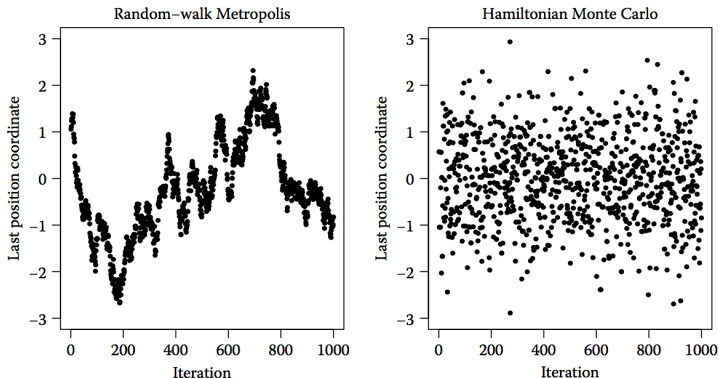
FIGURE 5.6
Values for the variable with largest standard deviation for the 100-dimensional example, from a random-walk Metropolis run and an HMC run with $L = 150$. To match computation time, 150 updates were counted as one iteration for random-walk Metropolis.

from RM Neal. MCMC Using Hamiltonian Dynamics (2011) [1]

HMC performance
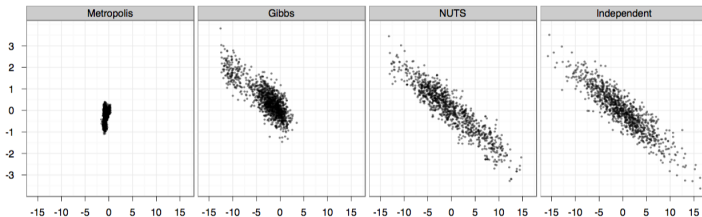
Figure 7: *Samples generated by random-walk Metropolis, Gibbs sampling, and NUTS. The plots compare 1,000 independent draws from a highly correlated 250-dimensional distribution (right) with 1,000,000 samples (thinned to 1,000 samples for display) generated by random-walk Metropolis (left), 1,000,000 samples (thinned to 1,000 samples for display) generated by Gibbs sampling (second from left), and 1,000 samples generated by NUTS (second from right). Only the first two dimensions are shown here.*

from MD Hoffman and A Gelman. The no-U-turn sampler: Adaptively setting path lengths in Hamiltonian Monte Carlo (2014) [2]

Also see: http://elevanth.org/blog/2017/11/28/build-a-better-markov-chain/

Overview of NONMEM implementations

- MAP estimation
  - Using prior distributions with any optimization method
- MCMC
  - METHOD = BAYES: Metropolis-Hastings within Gibbs sampling
  - METHOD = NUTS: No U-turn sampler (HMC with automatic optimization of sampling parameters)

Overview of NONMEM implementations

- MAP estimation
  - Using prior distributions with any optimization method
- MCMC
  - METHOD = BAYES: Metropolis-Hastings within Gibbs sampling
  - METHOD = NUTS: No U-turn sampler (HMC with automatic optimization of sampling parameters)
  - Remember:
    - MH (Metropolis-Hastings) is "meh"
    - Gibbs is "good"
    - HMC (NUTS) is "how maestros compute"

Brief discussion on prior distributions

- Think of prior distributions as part of the model.

See https://github.com/stan-dev/stan/wiki/
Prior-Choice-Recommendations

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- Priors should be chosen and subjected to scrutiny much like other model components.

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Brief discussion on prior distributions

- Think of prior distributions as part of the model.
- Priors should be chosen and subjected to scrutiny much like other model components.
- Model checking should ideally include sensitivity analysis of the priors.
- Choice of priors is most critical with sparse or limited data.

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What does it mean to be informative, uninformative or weakly informative?

Not well defined, but here's an attempt at some loose definitions:

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    - To capture prior knowledge
    - To challenge the analysis with competing points of view, e.g., use of pessimistic or optimistic priors.

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    - To capture prior knowledge
    - To challenge the analysis with competing points of view, e.g., use of pessimistic or optimistic priors.
- Uninformative prior: Ostensibly a prior that represents no information and therefore "let's the data tell the story."
    - E.g., a constant over the entire real line—an improper prior

Beware: That "uninformative" prior might not be!

- Suppose you use an improper prior for a standard deviation—a constant over the positive real line.
- That means all positive values are equally likely. Sounds like a reasonable definition of uninformative doesn't it?
- But that means that the prior assigns infinitely more probability to the set of values greater than any fixed value you care to choose.
- This will tend to bias the posterior to high values.
- Bottom line: A uniform distribution does not automatically confer uninformativeness.

Assessing convergence & adequacy of sample sizes

- Early samples may be unrepresentative of the target distribution
- MCMC samples within a chain are autocorrelated
  - Inferences based on MCMC samples are less precise than those from the same number of independent samples
  - Autocorrelation also influences the rate of convergence

Bayesian analysis in NONMEM

Assessing convergence & adequacy of sample sizes

Poor convergence & mixing

- Use a warmup phase, i.e., discard early iterations
- Monitor convergence via multiple chains with different starting points
  - Look for chains to converge to a common distribution
  - You want chain history plots to look more like straight horizontal "fuzzy caterpillars" than "wiggly snakes"
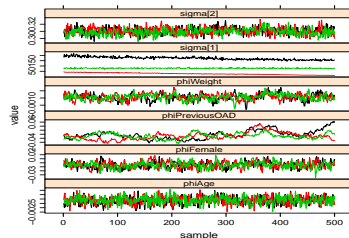
Good convergence & mixing
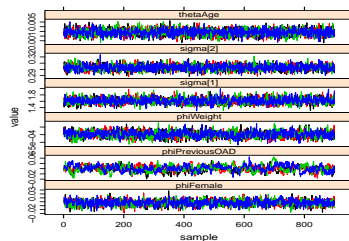
Assessing convergence & adequacy of sample sizes

- Gelman-Rubin diagnostics (Rhat or $\hat{R}$)
    - Essentially ratios of total variance to within chain variance.
    - Should approach 1 for all parameters of interest on convergence
- Effective sample size (ESS)
    - Measure of sampling efficiency
    - Bulk (location of distribution)
    - Tail (5th and 95th percentiles of distribution)
    - Desire ESS $> \approx 400$
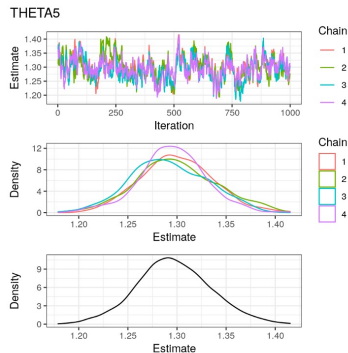
Bulk ESS = 188
Tail ESS = 354
Rhat = 1.01

Assessing convergence & adequacy of sample sizes

THETA1

- ESS vs draw
  - Will longer chains solve convergence issues?
- ESS vs quantile
  - Ensure convergence across all quantities of interest
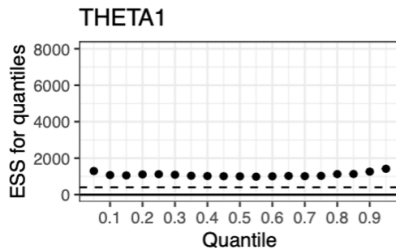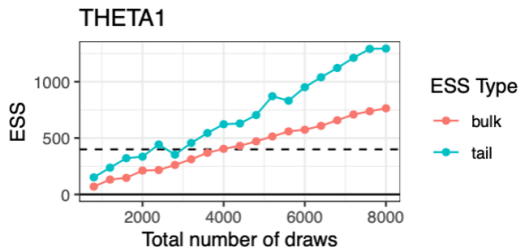
IMHO

- Do NOT trust automatic convergence detection to determine number of burn-in samples.
- In particular, do NOT use NONMEM's termination tests (CTYPE option) for terminating burn in.

When stuff goes wrong

- Diagnosing and remedying sampling problems encountered with MCMC
- Reparameterization, e.g., centered vs non-centered parameterizations for hierarchical models
- Prior distributions as part of the solution

Improving computational efficiency and sampling performance

The main strategies are:

- Reparameterization
- Adjusting MCMC tuning parameters
- Weakly informative priors to regularize fitting of hierarchical models

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- For example switch from centered to non-centered parameterization (or vice versa) of random effects in hierarchical models.
- Other reparameterizations that reduce posterior curvature and correlation, e.g., truncated Emax parameterization.
- Use MU referencing when possible with BAYES and NUTS.

Devil's funnel

Funnel Density (log scale)

log p(y,x[1])
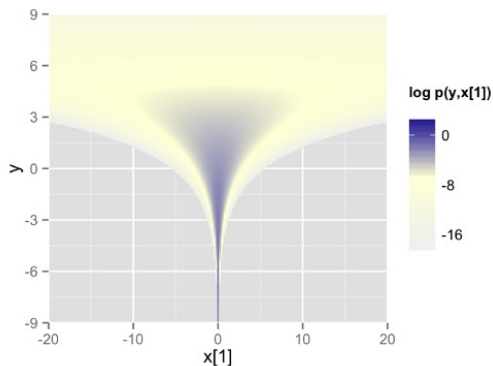
$$y \sim N(0, 3)$$
$$x \sim N(0, \exp(y/2))$$

Centered (CP) and non-centered (NCP) parameterization

Consider an individual parameter $\phi_i \sim N(\mu, \omega)$.

- CP refers to specifying ϕ_i directly using that distribution centered at μ.
- NCP refers to specifying ϕ_i indirectly using a standard normal, $\eta_{std,i} \sim N(0, 1)$, and then calculating $\phi_i = \mu + \omega\eta_{std,i}$
- The above is generalized to multivariate normal case using a Cholesky decomposition to generate a multivariate normal vector from standard normal ηs.

Centered (CP) and non-centered (NCP) parameterization in NONMEM

- For NUTS,
    - AUTO = 0 or 1 for CP
    - AUTO = 2 for NCP
    - AUTO = 3 for something in between. Uses $N(0, \omega)$ instead of $N(0, 1)$
- To my knowledge there are no equivalent implementations for BAYES.

Reparameterize to reduce correlation among parameters

PII-108

"TRUNCATED SIGMOID E_{max} MODELS": A REPARAMETERIZATION OF THE SIGMOID E_{max} MODEL FOR USE WITH TRUNCATED PK/PD DATA. WJ Bachman PhD and WR Gillespie PhD, GloboMax LLC, Hanover, MD.

The parameters of the sigmoid E_{max} model are poorly estimated when the range of PK/PD data available is limited to $<0.95E_{max}$ [Dutta et al. J Pharm Sci 85:232 (1996)]. The following reparameterized form of the sigmoid E_{max} model has improved parameter estimation properties:

$$E = E_0 + \frac{(\beta^\gamma + 1)(E^* - E_0)C^\gamma}{C^{*\gamma} + \beta^\gamma C^\gamma}$$

where E is the effect measure and C is a measure of drug exposure (e.g., concentration or dose). The parameter E^* is the estimated effect resulting from C^*, γ is the usual "sigmoidicity" parameter, and E_0 is the baseline effect. β is a measure of the degree to which the function deviates from linearity in C^γ. One approach to applying this parameterization is to fix C^* (or E^*) at a value and estimate the remaining parameters E_0, E^* (or C^*), β, and γ by nonlinear regression. The properties of this approach are evaluated by application to simulated PK/PD data that is truncated at various fractions of E_{max}. When C^* (or E^*) is chosen within the range of the observed data, then the parameters E^* (or C^*) and β are more precisely and accurately estimated than EC_{50} and E_{max} of the standard parameterization.

- With BAYES method high correlation among parameters often causes high autocorrelation in the MCMC samples.
- This often happens with asymptotic functions like the Emax function.
- NUTS is more robust to such correlation.

CP&T 63:199 (1998)

Prior distributions as part of the solution

IIV variances are difficult to estimate, particularly with data from a small number of individuals. What to do?

- Reduce the number of random effects until you find a set you can estimate with high precision, or
- Use a weakly informative prior for Ω that is consistent with our knowledge of IIV and excludes clearly implausible values.

I argue that for most PMX models the latter is more consistent with our knowledge and should be the preferred approach.

Other considerations for NONMEM

- Control stream
  - Priors
  - Initial estimates
- Diagnostics
  - MCMC diagnostics
  - Model diagnostics

NONMEM control stream

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  - Allow Gibbs sampling (vs MH) for `METHOD=BAYES`
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- Specify as many priors as possible

NONMEM control stream: priors for THETAs

- Normal distribution
  - Mean $THETAP
  - Variance $THETAPV
    - Shorthand:
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- t-distribution (METHOD=NUTS)
  - Set degrees of freedom in $EST TTDF or $TTDF

NONMEM control stream: priors for OMEGAs

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NONMEM parameterization of the inverse Wishart distribution

NONMEM implementation of inverse Wishart prior for Ω (or Σ):

$$\Omega \sim W^{-1}\left(\nu\Omega_{\text{prior}}, \nu\right)$$

$W^{-1} =$ Standard parameterization of the inverse Wishart

$\nu =$ degrees of freedom

$$E\left(\Omega\right) = \frac{\nu\Omega_{\text{prior}}}{\nu - n - 1}$$

$$\text{Var}\left(\Omega_{ii}\right) = \frac{E\left(\Omega_{ii}\right)\left(\nu - n - 1\right)}{\nu}$$

$$n = \dim\left(\Omega\right)$$

Inverse Wishart distribution

Guidance for setting *Omega*$_{\text{prior}}$ and ν:

$$\nu_i = \frac{2E\left(\Omega_{ii}\right)^2}{\text{Var}\left(\Omega_{ii}\right)} + n + 3$$

$$\Omega_{\text{prior},ii} = \frac{E\left(\Omega_{ii}\right)\left(\nu_i - n - 1\right)}{\nu_i}$$

- Set diagonal elements of Ω_{prior} to the calculated values of $\Omega_{\text{prior},ii}$
- Set $\nu = \min\left(\nu_i\right)$.

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  - OMEGA and SIGMA initial estimates from inverse Wishart distributions
    - Degrees of freedom from `DF` and `DFS`

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- Further post-processing is required to summarize and diagnose models **across all chains**

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- $TABLE outputs
  - ETA values not derived across posterior distribution, but post hoc estimates using mean of THETAs/OMEGAs
    - May result in spurious correlations

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Better to derive estimates/diagnostics using the full posterior: Shrinkage

- Shrinkage = $1 - \frac{SD_{k=1}^{K}(\overline{\eta_k})}{\sqrt{\overline{\Omega}}}$
  - $\overline{\eta_k}$ is mean of ETA posterior samples for subject k
  - $SD_{k=1}^{K}$ is standard deviation across K subjects
  - $\overline{\Omega}$ is mean of OMEGA estimates across posterior samples

Better to derive estimates/diagnostics using the full posterior: NPDE

- Can be calculated with npde R package
- Reuse output from PRED simulations:
$y_{ijs}^{\mathrm{sim,PRED}} \Rightarrow Y_i^{\mathrm{sim}(k)}$

$$\mathbf{Y}_i^{\mathrm{sim}(k)*} = \mathrm{var}(\mathbf{Y}_i)^{-1/2}(\mathbf{Y}_i^{\mathrm{sim}(k)} - E(\mathbf{Y}_i))$$

$$\mathbf{Y}_i^* = \mathrm{var}(\mathbf{Y}_i)^{-1/2}(\mathbf{Y}_i - E(\mathbf{Y}_i))$$

$$\mathrm{pde}_{ij} = F_{ij}^*(y_{ij}^*) \approx \frac{1}{K}\sum_{k=1}^{K}\delta_{ijk}^*$$

where $\delta_{ijk}^* = 1$ if $y_{ij}^{\mathrm{sim}(k)*} < y_{ij}^*$ and 0 otherwise.

[5]

Model selection criteria: what not to use

- Traditional objective function comparison not appropriate
- Alternatives: AIC, DIC, WAIC, cross-validation
  - AIC: not suitable for strong informative priors
  - DIC: unreliable for non-Gaussian posteriors
  - WAIC: not robust with weak priors or influential observations
  - Cross-validation: too computationally demanding

Model selection: Use PSIS-LOO

- PSIS: Pareto smoothed importance sampling
- LOO: leave-one-out cross-validation
  $$\widehat{\text{elpd}}_{\text{psis-loo}} = \sum_{i=1}^{n} \log \left(\frac{\sum_{s=1}^{S} w_i^s p(y_i|\theta^s)}{\sum_{s=1}^{S} w_i^s} \right)$$

- Available using `loo` R package
- $p(y_i|\theta^s)$ is likelihood for a subject or observation at a given posterior sample
  - Requires post hoc calculation with posterior ETAs

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- E.g., when you want your inferences to be informed by both prior information and new data.
- IMHO we should be using informative prior distributions more extensively, particularly during the "learn" stages of drug development.

Further reading

- Introduction to Bayesian pharmacometric data analysis with NONMEM (ACoP 2019 workshop by Bill Gillespie and Curtis Johnston)
- Bauer RJ. NONMEM Tutorial Part II: Estimation Methods and Advanced Examples. *CPT Pharmacometrics Syst Pharmacol.* 2019;8(8):538-556. doi:10.1002/psp4.12422
- Supplementary code for NONMEM Bayes tutorial paper (submitted):
  https://github.com/metrumresearchgroup/NMBayesTutorial

Example PK model

- 2-compartment PK model
- Several covariates on clearance
- GitHub repo with models/scripts (and these slides):
  https://github.com/timwaterhouse/iu-nonmem-bayes-2023

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